infringes a claim, it cannot be patentable over it (citing Eli Lilly and Company v. Generix Drug Sales, Inc., 324 F.Supp. 715, 169 USPQ 13 (S.D.Fla. 1971), affirmed in pertinent part 460 F.2d 1096, 174 USPQ 65 (5 Cir. 1972)). Apparently, the Examiner believes that because the Court in Lilly found that an enantiomer infringes a claim to a racemate, that enantiomer could not be patentable. Specifically, the Examiner looks to the flip side of the Court's holding and contends that "[i]f [an enantiomerically pure form of a compound] is patentable, then it would not constitute an infringement [of the previously patented racemic counterpart]". The Examiner is mistaken as a matter of law.

The error in the Examiner's interpretation of Lilly can be demonstrated in various ways. For example, no one can doubt that a species may be patentable as a selection over its genus due to surprising or unexpected properties. Yet, the species still infringes claims to the genus because, by definition, the species falls within the scope of the generic claims. When a patent to the species issues, the genus patent and the species patent are said to be "blocking patents" or "genus-species patents", i.e., neither patentee can practice the species invention without infringing the other's patent. The patent directed to the genus is said to "dominate" the patent directed to the species. The patent directed to the species is said to be an improvement or selection patent.

Genus-species patents were addressed in Rohm and Haas Co. v. Mobil Oil Corp., 462 F. Supp. 732, 201 USPQ 80 (D.Del. 1978) ("Rohm and Haas I"). Both Rohm and Haas and Mobil held United States patents directed to diphenyl ether herbicides, some of which were marketed by Rohm and Haas under the trade

name "Blazer". In Rohm and Haas I, the Court recognized the relationship as follows:

> "[T]he Mobil and Rohm & Haas patents are believed to stand in a genus-species relationship thus creating a classic 'blocking patent' situation so that neither Mobil nor Rohm and Haas can manufacture or sell Blazer compounds without infringing the other's patent...." Rohm and Haas I, 462 F.Supp. at 733, 201 USPQ at 81 (emphasis added).

After 12 years of litigation, the Delaware Court remained convinced of the species-genus relationship of these patents. Rohm and Haas Co. v. Mobil Oil Corp., 718 F.Supp. 274 (D.Del. 1989), affirmed without published opinion 895 F.2d 1421 (Fed.Cir. 1990) (Rohm and Haas II"):

> "[T]he parties here have blocking patents. That is, neither can practice its invention and avoid infringing the other's without a license." Rohm and Haas II, 718 F. Supp. at 285.

The Court also had no difficulty recognizing that both patents were presumed valid:

> "The parties bear a heavy burden here to prove that the patent claims asserted against them are invalid or unenforceable. Each patent in suit is presumed valid...." Id.

If the species claims were either invalid in their own right or non-infringing of the genus claims as Examiner Tsang asserts, why would the Court have entertained over 12 years of litigation? And why would the Court have emphasized the "heavy burden" to prove the species claims invalid?

Many other cases are in accord with Rohm and Haas I and Rohm and Haas II. For example, in In re Kaplan, 789 F.2d 1574, 229 USPQ 678 (Fed.Cir. 1986), the Court of Appeals for the Federal Circuit reversed a double patenting rejection stating that the Board of Patent Appeals and Interferences had "confused double patenting with 'domination'." Kaplan, 789 F.2d at 1577, 229 USPQ at 681. The CAFC went on to explain the distinction:

> "By domination we refer, in accordance with established patent law terminology, to that

> phenomenon, which grows out of the fact that patents have claims, where-under one patent has a broad or 'generic' claim which 'reads on' an invention defined by a narrower or more specific claim in another patent, the former 'dominating' the latter because the more narrowly claimed invention cannot be practiced without infringing the broader claim...." 789 F.2d at 1577, 229 USPQ at 681.

The CAFC did not say that the narrower invention is not patentable. It assumes that a valid patent has issued on the narrower invention. Nor did the CAFC say that the narrow invention, being patentable, cannot not infringe the broader claims. It clearly held that the narrower invention cannot be practiced because it would infringe the broad claim of the "dominating" patent.

In In re Baird, 16 F.3d 380, 29 USPQ 1550 (Fed.Cir. 1994), the CAFC said much the same:

> "The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious...." 16 F.3d at 382, 29 USPQ2d at 1552.

Apposite also is In re Jones, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed.Cir. 1992). There the CAFC held a claimed salt, which was admittedly encompassed by a genus disclosed in a prior art reference, patentable.

For the convenience of the Examiner, applicants have provided copies of Rohm and Haas I, Rohm and Haas II, Kaplan, Baird and Jones. These, as well as many other cases conforming to their analysis, support applicants' assertion that a species claim encompassed by a generic claim of an issued patent may be patentable over that patent even if it infringes the generic claim. The fundamental reason for this is that a patent is a grant of the right to exclude others from making, using or selling the claimed invention. Two parties may possess overlapping rights to exclude.

Nothing in Lilly contradicts or questions this law. Lilly simply does not address the issue of patentability of the species compound. The infringement analysis in Lilly is irrelevant to the patentability of the specific enantiomer in that case or the claims of this application. Accordingly, applicants request that the Examiner reconsider and withdraw her first argument.

Next, the Examiner argues that the (-)-enantiomer of this invention is not patentable because EP-382,526 and United States patent 5,047,407 "implicitly and inherently made available the four enantiomers". Furthermore, the Examiner contends that "it is common knowledge that optical isomers differ in their pharmacological action" and that "it is routine to find out which [optical isomer] contributes the activity [sic]". Presumably, this contention has led the Examiner to conclude that the claims are unpatentable even though she concedes that "[t]he finding [that the] non-natural (-)-enantiomer is as active as the natural (+)-enantiomer is surprising". Applicants traverse the rejection.

Patentability of single enantiomers over the corresponding racemate has already been addressed at length in applicants' July 23, 1993 response. In that response, applicants presented case law supporting their position that, as a matter of law, a single enantiomer which is not specifically disclosed in prior art is patentable over the corresponding racemate, provided that the enantiomer possesses unexpectedly beneficial properties. Application of Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963); In re Chupp, 816 F.2d 643, 2 USPQ2d 1437 (Fed.Cir. 1987); Brenner v. Ladd, 247 F.Supp. 51, 147 USPQ 87 (D.D.C. 1965). Applicants incorporate those arguments here. In addition, applicants expand those arguments to demonstrate

that other precedence also supports the patentability of the claims.

It is a well settled principle in patent law that the existence of a compound as an ingredient of another substance does not negate novelty in a claim to the pure compound. Application of Williams, 171 F.2d 319, 80 USPQ 150 (CCPA 1948) (copy enclosed). In Williams, the appealed claim recited the "laevo rotary form ... 'substantially free from the dextro rotary form'" whereas the prior art publication disclosed a racemic mixture. The Board had decided that the racemic mixture "necessarily contains both dextro rotary and laevo rotary components" and that "the laevo rotary compound [i.e., the (-)-enantiomer], having existed as part of the racemic mixture, cannot be novel" (not unlike the argument of Examiner Tsang in rejecting the claims of this application). 171 F.2d at 320, 80 USPQ at 151. The CCPA, however, overturned the Board and held that the single enantiomer was novel. Id.

It is also well settled law that compounds which possess superior or unexpected properties are not obvious over an impure mixture containing the claimed compound. Sterling Drug v. Watson, 135 F.Supp. 173, 108 USPQ 37 (D.D.C. 1955) (copy enclosed). In Sterling, the District Court reversed a Board decision rejecting claims to l-arterenol and salts thereof substantially free from d-arterenol for lack of invention because the corresponding racemate was old. The Board had reasoned that:

> "'[T]he Karrer textbook, in the third paragraph, page 91 discloses that racemic mixtures break down in solution into their optically active isomers, and since Stolz et al. disclose salts of arterenol in solution each optical isomer must have existed in said solution as an entity in itself. In view of the known fact ... that racemic mixtures may be resolved into their optically active isomeric components, we are of the view that appellant's isolated optical isomeric

compounds are not patentable.'" Sterling, 135 F.Supp. at 175, 108 USPQ at 38.

The District Court was not convinced. It held the claims patentable. Specifically it pointed to the unexpected therapeutic properties of l-arterenol (much like the properties relied upon by applicants in the present application):

> "[T]here can hardly be any serious question that these beneficial characteristics were both unexpected and unobvious, which is the test to be applied in the matter of the patentability of a compound that is a homologue of another.
>
> * * *
>
> I have no hesitancy in reaching the firm conclusion that the l-arterenol, as set forth in claim 10, and the acid salt of l-arterenol in claim 12 and the l-arterenol acid d-tartrate, as set forth in claim 14, are patentable...." 135 F.Supp at 176, 108 USPQ at 38-39.

Particularly noteworthy is the CCPA's analysis of the patentability of single enantiomers in Application of May, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (copy enclosed). In May, the CCPA considered the patentability of enantiomerically enriched benzomorphan analgesics whose racemic counterparts were known analgesics. The prior art disclosed that the analgesic activity of benzomorphans resided chiefly in the claimed laevo enantiomer and that optical isomers of benzomorphans could be separated. Still, the CCPA held the claimed laevo enantiomer patentable. The CCPA began its analysis of the composition claims by noting "that [the] claims ... recite a novel compound. In re Williams, supra." May, 574 F.2d at 1093, 197 USPQ at 610 (emphasis in original). The CCPA then went on to say:

> "[M]erely because those skilled in the art would have expected the [laevo enantiomer] to have analgesic activity, does not mean, as the board apparently suggests, that an irrebuttable presumption of obviousness has been established. Those properties which would have been expected must be balanced against the unexpected properties...." 574 F.Supp at 1094, 197 USPQ at 610 (emphasis in original).

Upon considering affidavits submitted by appellants setting forth the unexpected properties of the claimed enantiomer, the

CCPA concluded that claims directed to the laevo enantiomer were patentable.

These decisions set forth the standards by which the patentability of single enantiomers must be judged. The standard is one of unexpected or surprising activity compared to the racemate. That the corresponding racemate was known is irrelevant so long as the claimed enantiomer possesses surprising beneficial properties. It is also irrelevant that the separation of the enantiomers was within the skill of the art. May even suggests that a teaching to separate the claimed enantiomer can be cast aside. What truly matters is whether or not the claimed enantiomer has unexpected properties.

Here, the Examiner has conceded that applicants' discovery of antiviral activity in the "non-natural" (-)-enantiomer of this invention "is surprising". Applicants have also provided scientific articles and the Declaration of Dr. Richard Storer, an expert in the field of antiviral nucleosides (filed with applicants' March 15, 1994 response). Both demonstrate the unexpected nature of the activity and low toxicity of the claimed (-)-enantiomer. The cited articles and Dr. Storer's declaration also explain how these unexpected properties translate to a surprisingly high and beneficial therapeutic index for the claimed enantiomer. The Examiner, on the other hand, has provided no evidence to rebut or refute this demonstration. In short, the Examiner has no valid basis -- legal or factual -- for her rejection. Accordingly, applicants request that the rejection under 35 U.S.C. §§ 102 and 103 over EP-382,526 and United States patent 5,047,407 be withdrawn.

The Examiner has also maintained the rejection of claims 3-5, 10, 21 and 22 under 35 U.S.C. §§ 102 and 103 over United States patent 5,204,466 without providing any reasons as

to why applicants' March 15, 1994 or applicants' July 22, 1994 response and arguments against that rejection were not deemed convincing. In any event, applicants traverse this rejection. United States patent 5,204,466, like United States patent 5,047,407, refers to no more than a racemic form of the enantiomer claimed in this application. The reference to "enantiomerically enriched" compounds in United States patent 5,204,466 is meaningless. United States patent 5,204,466 does not specifically identify which enantiomer is important. In fact, United States patent 5,204,466 actually leads the skilled reader to believe that it is the (+)-enantiomer that is intended (See applicants' July 22, 1994 Response to Final Office Action, pp. 2-4). The claimed enantiomer is, thus patentable over the '466 patent for the very same reasons that it is patentable over United States patent 5,047,407. Accordingly, applicants request that the Examiner withdraw the rejection.

The Examiner has stated "the in vitro assays are not predictive of in vivo efficacy" and invited applicants to submit clinical data to demonstrate in vivo efficacy of the claimed compounds. Although the Examiner has not made a rejection under a specific statute, applicants believe the Examiner intended to reject the claims under 35 U.S.C. § 101.

Applicants hereby submit a copy of Commissioner Lehman's Guidelines for Examination of Applications for Compliance with the Utility Requirement published in the Federal Register on January 3, 1995 and the accompanying legal analysis of the law governing 35 U.S.C. § 101 prepared by the United States Patent and Trademark Office. Under the new guidelines, to properly reject a claim under § 101, the Examiner must (a) make a prima facie showing that the claimed invention lacks utility and (b) provide a sufficient evidentiary basis for

factual assumptions relied upon in establishing the prima facie showing. Further, the prima facie showing must be set forth in a well reasoned statement in which the Examiner articulates sound reasons why a person of ordinary skill in the art would conclude that it is more likely than not that an asserted utility is not credible. And, the statement should specifically identify the scientific basis of the Examiner's conclusions.

The Examiner has not made such a prima facie showing, nor has she provided any evidentiary or scientific basis for the rejection. On that ground alone, she should withdraw the rejection.

Applicants, however, have gone further here. They have actually conducted phase I, II, and II clinical trials of the claimed compounds. Those trials are described in the attached scientific publications and news articles. These publications and articles demonstrate that the claimed compounds are effective in the in vivo treatment of HIV and hepatitis B virus infections. Under the legal analysis of the law governing 35 U.S.C. § 101 prepared by the United States Patent and Trademark Office, such trials, by definition, establish utility.

Accordingly, in view of the in vitro data provided in the specification, the Declaration of Richard Storer Under 37 C.F.R. § 1.132 submitted in response to the September 15, 1993 Office Action and the scientific and news articles submitted concurrently herewith evidencing the in vivo efficacy of the claimed compound, the Examiner must withdraw this rejection.

For the foregoing reasons, applicants believe that the claims are in condition for allowance and request that the Examiner withdraw all rejections and allow this application.

Respectfully submitted,

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I Hereby Certify that this Correspondence is being Deposited with the U. S. Postal Service as First Class Mail in an Envelope Addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on January 13, 1995

Thomas Quinlan
Name of Person Signing

Signature of Person Signing